Laboratory diagnosis of HAE: is there a role for molecular analysis in routine clinical practice?

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Diagnosis of hereditary angioedema (HAE) is made in presence of a family history of recurrent angioedema or in presence of an inherited deficiency of C1 inhibitor in a patient with recurrent angioedema. Although in the majority of patients hereditary angioedema is the clinical phenotype of inherited C1 inhibitor deficiency, there are patients with well proved family history of angioedema and normal C1 inhibitor and a few subjects with angioedema who inherited C1 inhibitor deficiency from one parent with the same defect, but clinically asymptomatic.

In order to appropriately cover all diagnosis of HAE, it is necessary to combine clinical and laboratory data: while the clinical symptoms that identify HAE are obvious, there is no consensus on the biochemical and genetic laboratory tests confirming the diagnosis. C1 inhibitor deficiency is the only laboratory abnormality strongly associated with angioedema and the most frequent cause of C1 inhibitor deficiency are mutations in C1 inhibitor gene (SERPING1) that modify the protein structure. Mutations in Factor XII are detected in HAE with normal C1 inhibitor, though with incomplete penetrance and without established definition of the attending protein defect.

Laboratory testing in a patient with hereditary angioedema symptoms should first be aimed to identifying the deficiency of C1 inhibitor protein and the attaining reduction of the fourth component of complement (C4). When both C1 inhibitor and C4 are below 50% of normal values, diagnosis of HAE type I with C1 inhibitor deficiency is established without need for further testing. To reach 100% of diagnosis of HAE with C1 inhibitor deficiency, measurement of C1 inhibitor function is required for those patients with HAE, normal C1 inhibitor protein and low C4. This measurement is usually best obtained using a chromogenic assay that determines the capacity of plasma C1 inhibitor to inhibit a fixed amount of C1s. In presence of normal C1 inhibitor protein and C4 above 50% of normal value, it is highly questionable the real need for functional measurement of C1 inhibitor. In our case list of 634 patients with HAE with C1 inhibitor deficiency only one had C4 above 50% of normal.

Genetic testing for diagnosing HAE with C1 inhibitor deficiency in routine clinical practice has limited, but important indications and the technical drawback of the need for sequencing the entire gene since almost any family has a different mutation. Recognizing the mutation underlying C1 inhibitor deficiency is relevant when the inheritance pattern of the disease cannot be assessed by family history. Genotyping in these patients is necessary to distinguishing *de novo* mutations, detected in 25% of newly diagnosed HAE patients with C1 inhibitor deficiency, from acquired C1 inhibitor deficiency. Demonstration of a genetic defect is mainly relevant for genetic counseling determining if the deficiency can be transmitted to the offspring. Genotyping is also necessary whenever prenatal diagnosis is required. Such a diagnosis in HAE with C1 inhibitor deficiency is provided by evidence that the fetus carries the disease-causing mutation detected in the affected parent.

In HAE with normal C1 inhibitor, genetic analysis can ascertain a mutation in FXII. Detecting such mutation is clinically relevant because it enables to identifying asymptomatic carriers at risk for transmitting the disease to their offspring.